

# Smoking and ulcer perforation

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## Abstract

**Background**—The use of ulcerogenic drugs is the only well documented risk factor for peptic ulcer perforation, but accounts for only a quarter of the events. Smoking is a well known risk factor for uncomplicated ulcer disease, and patients with ulcer bleeding have increased death rates from smoking related disorders.

**Aim**—To assess the role of smoking in ulcer perforation.

**Subjects**—A total of 168 consecutive patients with gastroduodenal ulcer perforation and 4469 control subjects from a population based health survey.

**Methods**—The association between ulcer perforation and smoking habits was analysed by logistic regression while adjusting for age and sex.

**Results**—Current smoking increased the risk for ulcer perforation 10-fold in the age group 15–74 years (OR 9.7, 95% CI 5.9 to 15.8) and there was a highly significant dose-response relationship ( $p < 0.001$ ). The results were similar in men (OR 9.3, 95% CI 4.9 to 17) and women (OR 11.6, 95% CI 5.3 to 25), and for gastric (OR 10.5, 95% CI 4.5 to 25) and duodenal (OR 8.6, 95% CI 4.9 to 15.4) ulcer perforation. No increase in risk was found in previous smokers (OR 0.8, 95% CI 0.2 to 2.2).

**Conclusion**—Our findings suggest that smoking is a causal factor for ulcer perforation and accounts for a major part of ulcer perforations in the population aged less than 75 years.

(Gut 1997; 41: 177–180)

**Keywords:** peptic ulcer perforation; gastric ulcer; duodenal ulcer; smoking; NSAID; risk factor

The aetiology of the majority of ulcer perforations is not known. Current use of non-steroidal anti-inflammatory drugs (NSAIDs) has been shown to increase the risk for ulcer perforation 6–8 times, and seems to account for about a quarter of the events.<sup>1,2</sup> The role of *Helicobacter pylori* infection in ulcer perforation is uncertain. In a study of patients with acute perforated duodenal ulcer the infection was as common among patients as among hospital controls.<sup>3</sup> However, smoking prevalences of 84% and 86% have been reported among patients with duodenal ulcer perforation,<sup>3,4</sup> and smokers have a threefold higher mortality from peptic ulcer than non-smokers.<sup>5</sup> The purpose of the present study was to assess the role of cigarette smoking in ulcer perforation.



Figure 1: Shaded areas are Hordaland and Rogaland counties in western Norway.

## Methods

### PATIENTS

One hundred and seventy five consecutive patients with ulcer perforation admitted to three surgical departments in western Norway between July 1987 and June 1991 were included. The diagnosis was confirmed by operation (170 patients) or by necropsy (five patients). Structured interviews were performed by the authors (CS, JAS, AS, and BTS). One hundred and thirty eight patients (79%) were successfully interviewed in hospital while 22 patients (13%) were interviewed by telephone after discharge. Information on smoking habits was ascertained from relatives for eight of 15 patients who co-operated poorly (13, who all eventually died, due to poor general condition; two due to mental disturbances). Data on smoking habits were therefore available for 168 out of 175 patients (96%). The patients were asked whether they smoked at the time of perforation. Patients answering "yes" ( $n=107$ ) were asked how many cigarettes, pipes, and/or cigars they smoked daily. A total of 102 patients reported daily cigarette smoking, seven patients smoked only

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Accepted for publication  
10 March 1997

TABLE 1 Previous medical history and use of drugs and alcohol in 168 patients with perforated peptic ulcer in western Norway 1987–1991

	Age 15–74 years (n=118)		Age 75–94 years (n=50)	
	Non-smokers (n=23)	Current smokers (n=95)	Non-smokers (n=38)	Current smokers (n=12)
Number (%) women	11 (48%)	28 (30%) <sup>†</sup>	25 (66%)	1 (8%)*
Associated severe disease last year	10 (44%)	16 (17%)*	13 (38%)	3 (25%)
Previous peptic ulcer‡	8 (38%)	41 (45%)	13 (35%)	7 (58%)
Previous ulcer dyspepsia	13 (87%)	80 (96%)	20 (83%)	8 (89%)
Previous ulcer complications§	6 (29%)	11 (12%) <sup>†</sup>	6 (16%)	4 (33%)
Ulcerogenic drugs ¶**	12 (52%)	15 (16%)*	10 (29%)	3 (25%)
NSAIDs **	7 (32%)	8 (9%)*	6 (17%)	1 (8%)
Others **	7 (30%)	6 (7%)*	6 (17%)	2 (17%)
Non-ulcerogenic drugs**	17 (77%)	48 (52%) <sup>†</sup>	25 (71%)	7 (58%)
Large consumption of alcohol††	1 (4%)	24 (25%)*	1	1

\* p&lt;0.05 (adjusted for age and sex in logistic regression analysis).

† p&gt;0.05 and ≤0.1 (adjusted for age and sex in logistic regression analysis).

‡ Verified by radiological imaging, endoscopy, or operation.

§ Ulcer perforation, ulcer bleeding treated with blood transfusion or hospitalisation due to pyloric stenosis.

¶ NSAIDs, aspirin and/or steroids.

\*\* Any intake within the last 8 weeks prior to perforation.

†† Daily use or ≥15 units of alcohol during last 14 days (80th percentile).

TABLE 2 Cigarette smoking and ulcer perforation in western Norway. The odds ratios, referring to current smoking versus non-smoking, are adjusted for age and sex by multiple logistic regression analyses

	Number		Current smokers (%)		Odds ratio (95% CI)
	Patients	Controls	Patients	Controls	
All patients 15–74 years	109	4270	80	37	9.7 (5.9–15.8)
Men	72	2119	83	40	9.3 (4.9–17)
15–59 years	44	1814	93	41	21.0 (6.0–69)
60–74 years	28	305	68	33	4.7 (2.0–10.9)
Women	37	2151	73	34	11.6 (5.3–25)
15–59 years	14	1787	79	38	7.3 (2.0–26.6)
60–74 years	23	364	70	16	21.4 (7.4–62)
Gastric perforation	36	4270	81	37	10.5 (4.5–24.7)
Duodenal perforation	73	4270	78	37	8.6 (4.9–15.4)

a pipe or cigars. Patients answering “no” were asked whether they had ever smoked and, if “yes” (n=18), when they stopped smoking. Information on ulcer site was obtained from operation records. The perforations were classified as duodenal (including the pyloric orifice) or gastric (including the praepyloric area).

#### CONTROLS

Patients were retrospectively compared with participants in a population-based health survey conducted in Hordaland County, Norway in 1985.<sup>6</sup> A postal questionnaire was sent to a random sample of 4992 persons aged 15–73 years, of whom 90% responded. The control subjects were asked whether they smoked cigarettes daily at present, how many cigarettes they smoked daily, and whether they had smoked before.<sup>6</sup> Hordaland County includes the catchment area of two of the hospitals recruiting patients, while the third hospital was located in the neighbouring county of Rogaland (fig 1).

#### DEFINITIONS OF SMOKING HABITS

Current smokers were defined as persons who smoked daily at the time of perforation or at the time of the population survey. Ex-smokers were persons who had smoked daily and had given it up, while never-smokers were persons who had never smoked daily. Non-smokers were persons who did not smoke daily at the time of the perforation/survey, including ex-smokers and never-smokers. In analyses comparing patients

and controls, those who smoked only a pipe or cigars were excluded.

#### STATISTICAL METHODS

The relation of smoking habits to disease status, with adjustment for age (five year age groups) and sex, was studied using multiple logistic regression analysis. For trend analysis smoking was coded as: 1 (never-smoker), 2 (ex-smoker), 3 (1–9 cigarettes daily), 4 (10–19 cigarettes daily), and 5 (20+ cigarettes daily). The odds ratios approximated relative risks since ulcer perforation is a rare disease. Population attributable risk (PAR%) was calculated as follows:<sup>7</sup>

$$\text{PAR\%} = (P_e) (RR-1) / ((P_e) (RR-1) + 1) \times 100$$

where  $P_e$  is the proportion of smokers in the population and RR the relative risk of having an ulcer perforation.

#### Results

Among the patients, 80% in the age group 15–74 years were current smokers, while in the older subjects the smoking rate was 24%. Patients who were smokers suffered from other severe diseases more rarely and used NSAIDs or other ulcerogenic drugs less often (table 1). On the other hand, smokers more often had a high alcohol consumption. Thirteen patients considered to have alcohol problems were all current smokers. There were no significant differences in previous ulcer history.

TABLE 3 Ulcer perforation and increasing levels of cigarette smoking in the age group 15–74 years in western Norway. The odds ratios are adjusted for age and sex by multiple logistic regression analyses

	Patients	Controls	Odds ratio (95% CI)
Never smoked	14 (13%)	1819 (42%)	1
Ex smokers	8 (7%)	882 (21%)	0.8 (0.2–2.2)
1–9 cigarettes daily	17 (16%)	321 (7%)	7.3 (4.0–18.1)
10–19 cigarettes daily	44 (40%)	880 (21%)	8.7 (5.5–14.4)
≥20 cigarettes daily	26 (24%)	368 (9%)	11.2 (6.3–27.5)
Total	109 (100%)	4270 (100%)	

In the general population aged 15–74 years 37% were daily cigarette smokers compared with 80% among patients (table 2). Adjusting for differences according to age and sex, ulcer perforation was estimated to be 9.7 times more common in daily cigarette smokers than in non-smokers (95% CI 5.9 to 15.8) (table 2). The increase in risk was similar for men and women, and for gastric and duodenal ulcer perforation. According to these models, it was estimated that 76% (95% CI 64 to 85) of ulcer perforations in the population aged 15–74 years could be attributed to daily cigarette smoking. The population attributable risks were similar for men (77%) and women (78%).

The risk for ulcer perforation increased with the number of cigarettes smoked daily (table 3), with a highly significant trend ( $p < 0.001$ ). No association was found with former smoking. In the age group 15–74 years there were only 13% never-smokers among patients compared with 42% in the general population.

In patients aged 75 years or older smoking was not common and smoking habits differed markedly between the sexes. There was only one current smoker (4%) among the female patients in this age group, and 23 of the 26 women (88%) had never smoked. In the male patients 11 out of 24 (46%) were current smokers. A population study of men in Hordaland in 1990 reported 23% current smokers in this age group,<sup>8</sup> so an association between smoking and ulcer perforation is also suggested among men in this age group (OR 2.6, 95% CI 1.2 to 5.8). However, it was estimated that only 28% (95% CI 4 to 52) of the ulcer perforations in men aged 75 years or more could be attributed to smoking.

### Discussion

The present study suggests that most ulcer perforations among persons aged less than 75 years are caused by smoking. We found a very strong association between current cigarette smoking and ulcer perforation, the strength of the association was consistent between subgroups, and there was a significant dose-response relationship.

The results of the present study are subject to many potential biases. The usual problem of bias in the selection of the controls could, however, be kept to a minimum as data from a population survey with a high response rate were used for control purposes. Bias related to selection of cases also seems unlikely. Ulcer perforation is a disease where all patients are admitted to hospital because of the severity of symptoms and the relatively long time lag

between perforation and death. The diagnosis can be verified by operation or necropsy.

Different methods of data collection for cases and controls is a potential problem in this study. The main results (OR<sub>15–74 years</sub> 9.7; OR<sub>men</sub> 9.3; OR<sub>women</sub> 11.6) were thus cross-checked using information from national interview surveys.<sup>9</sup> This gave strikingly similar results (OR<sub>15–74 years</sub> 9.3; OR<sub>men</sub> 9.3; OR<sub>women</sub> 9.2). A community study in England suggested that self-reported smoking prevalences in population studies were underestimated by 3%.<sup>10</sup> Given that smoking in the present study was 3% underestimated among controls and 3% overestimated among patients, the crude odds ratio (not adjusted for age and sex) would decrease from 6.8 to 5.0, which still leaves a very strong association between ulcer perforation and smoking.

The population survey used as the control population was conducted in 1985, which is 2–6 years before the case collection. During this period of time smoking prevalences in Norway have decreased among men and remained unchanged among women.<sup>9</sup> Thus, this time difference could lead to an underestimation of the association between smoking and ulcer perforation. The data on male patients were re-analysed using control data from a questionnaire survey of Hordaland men conducted in 1990,<sup>8</sup> which gave an age-adjusted odds ratio of 9.9.

Theoretically, smoking could be a marker for other differences between cases and controls. Among the patients, 52% of the non-smokers had used ulcerogenic drugs and 48% had other severe diseases. In patients who were smokers other risk factors were rarely identified except for a higher use of alcohol. Such data were not available for the control population, so the influence of these factors on the association between smoking and ulcer perforation could not be adjusted for. Based on the information on patients, one might suspect that adjustment for use of NSAIDs would have resulted in an even stronger association between smoking and ulcer perforation.

The association between ulcer perforation and smoking seems biologically plausible. Smoking is known to have several adverse effects on the upper gastrointestinal tract.<sup>11</sup> Of particular interest for ulcer perforation is the finding that smoking causes immediate vasoconstriction in the mucosa.<sup>12</sup> Ischaemia reduces mucosal resistance<sup>13</sup> against, for instance, the action of acid and may thus contribute to ulcer perforation. This mechanism could explain why we observe an increased risk in current smokers but not in former smokers.

In elderly persons smoking seemed to be of less importance than in the younger age group. A previous study showed higher excess mortality after ulcer perforation in persons born after 1910.<sup>14</sup> These findings may suggest a shift in the aetiology of ulcer perforation over time, with smoking having a more predominant role in younger generations.

Tobacco smoking is a well known risk factor for uncomplicated peptic ulcer.<sup>15–17</sup> Smokers

have an increased risk for dying from peptic ulcer disease<sup>4</sup> and increased death rates from smoking-related disorders have been reported in patients with ulcer bleeding.<sup>18</sup> The present study strongly suggests that most ulcer perforations are related to smoking. The focus on NSAIDs in the aetiology of peptic ulcer disease seems appropriate as the complications relating to NSAID usage are iatrogenic. However, the findings of this study suggest that the incidence of ulcer perforation can only be markedly reduced, on a population basis, by smoking prevention.

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